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Applicant(s):	Mauriac et al.	Confirmation No.:	8762
Serial No.:	10/562,763	Art Unit:	1615
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Title:	"Subcutaneous implants having limited initial release of the active principle and subsequent linearly varying extended release thereof"		

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Commissioner for Patents
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DECLARATION UNDER 37 C.F.R. § 1.132

I, Patrice Mauriac, being duly sworn depose and say that:

1. I am a French citizen residing at: Paris (FR)
2. I am familiar with the English language

I further declare that I am one of the inventors and one of the Applicants of the current US patent Application.

I'm currently holding the R&D Director position at Laboratoires Leurquin Mediolanum, a French Pharmaceutical Company located in Neuilly sur Marne (France). Being a Doctor of Pharmacy and an Analytical Chemist (M Sc) by education, I have been working for more than 15 years in the Pharmaceutical Chemistry Manufacturing and Control field with a main focus on long term parenteral depots formulations over the last 10 years.

Chou et al. disclose a PCL or PVAC matrix while a coating of PLGA or EVA is applied by coextrusion. More clearly, the Figures provided in this document refer to:

- the release of flucinolone acetonide (FA) from PCL matrix, drug loading 75% (Fig. 1),
- the release of flucinolone acetonide (FA) from PLGA matrix, drug loading 60% (Fig. 2).

From said Figures, it is shown that **PCL matrixes** (Fig. 1) provide for a **far better release profile** when compared to PLGA matrixes (Fig. 2), even more so if considering that the drug loading in the latter case is reduced with respect with the first one. This means that PCL (being more hydrophobic than PLGA) provides for a better control of the release of the (hydrophobic) active ingredient used, i.e. FA. In this regard, the matrixes containing PCL have been selected by Chou et al. for making implants, and not containing PLGA.

At par. [0035] of Chou et al., it is stated that "the burst release phase was less pronounced when FA levels (loading) in the PCL matrix were reduced from 75% to 60% or 40%".

Having regard to the above, a skilled person would have never considered to use PLGA as matrix polymer for long term release implants.

However, if the same had tried to follow the teaching of Chou et al. other than using PLGA in place of PCL, further decreasing the drug loading, he/she would have supposed as follows.

The following tests had been carried out under my own responsibility.

Experimental section

1. Preparation of PLGA-drug matrixes

Three cylinder-shaped matrixes have been prepared by extrusion having the following compositions:

	Drug (Avorelin)	PLGA (L/G molar ratio 75/25 - molecular weight 115 kg/mol)
1	20% m/m	80% m/m
2	28% m/m	72% m/m
3	35% m/m	65% m/m

2. Evaluation of the drug release profile

The above matrixes have been tested in order to evaluate the drug release profile over the time, by comparing three different drug loadings.

Results

The drug release profile for the above three matrixes are showed in the following Figure A:

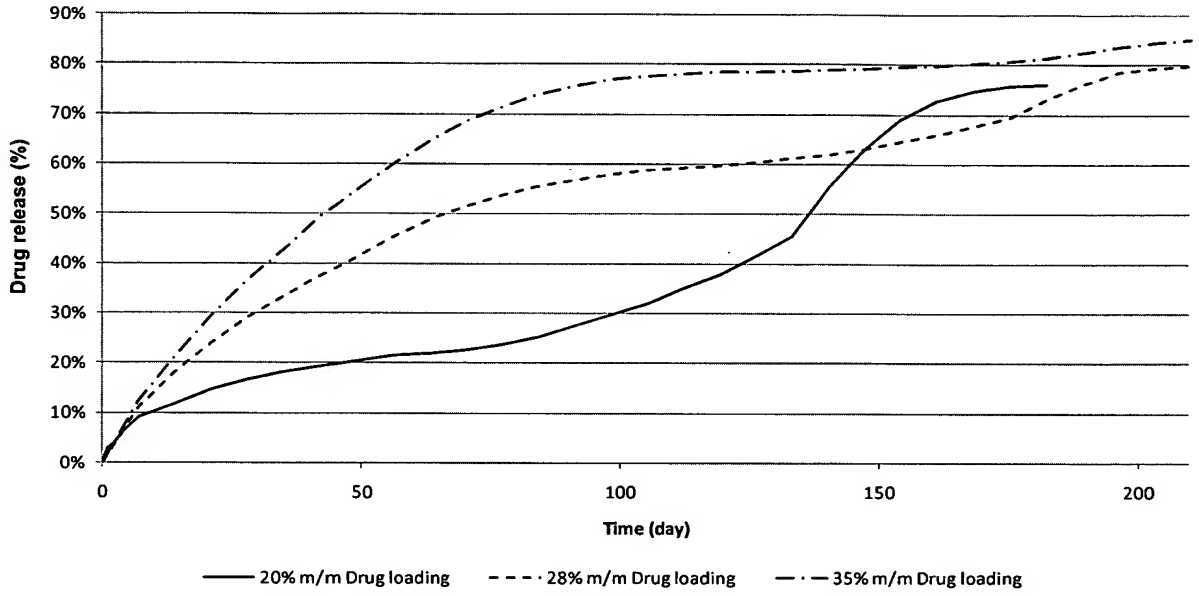

Figure A

From Figure A, it can be observed that:

- the drug is released (and the polymeric matrix is fully destroyed) in about 200 days when drug loading is comprised between 28% m/m and 35% m/m;

- by **decreasing the percentage of drug** within the matrix, a decreasing of the initial release rate occurs. This is not a surprise as diffusion rate is known to depend on the concentration **but,**

- the decrease of the initial release rate later results in a **sooner and bigger second burst,** thus leading to a **tri-phase release pattern limited to 160 days,** as clear when a drug loading of 20% m/m is used;

- without wishing to be bound by any theory, it is believed that this is due to the chemistry of polyesters which produce acidic residues when the chains are hydrolyzed. If a large amount of drug is released from the matrix, then a large amount of outer medium penetrates in the matrix and simultaneously helps in getting these acidic residues out of the matrix itself. On the other hand, if a few drug leaves the core during the early times, accordingly a few acidic residues will leave the core, they will stay inside and help in cutting the remaining ester bonds (phenomenon called auto-catalysis).

Therefore, in view of the above, it can be observed that:

- when a **lower drug loading** is used, as in Figure A, where the PLGA matrixes have a drug loading of 35%, 28%, 20% respectively, the first burst is progressively reduced while undesirably a **second burst** progressively occurs soon and big.
- this reduction of the initial diffusion rate finally leads to a **shorter overall release duration** caused by an undesired sooner destruction of the polymeric matrix.

In this regard, it is evident that the skilled person would have been led to avoid the use of PLGA as polymer matrix, since the above evidences clearly discourage from using the same. As a matter of fact, the skilled man would indeed been aware of the fact that PLGA is not a suitable matrix polymer for long term release implants.

Moreover, it should be noticed that Chou et al. only teach to prefer PCL as polymer for matrix, for reducing the first burst effect, by only disclosing PCL matrixes having drug loading of 75%, 60% and 40%, therefore, nothing useful is given to the skilled person for modifying this teaching in the direction of the current invention.

Chou et al. also disclose to coat the PCL/FA core with PLGA, particularly:

- describing the release of flucinolone acetonide (FA) from PCL matrix, with and without PLGA skin, drug loading 60% (Fig. 3), and
- describing the release of flucinolone acetonide (FA) from PCL matrix, with and without PLGA skin, drug loading 40% (Fig. 4).

Even more so, the skilled person, having regard to the results shown in Figure A and above discussed, would have been led to believe that, in the hypothetical case a PLGA matrix coated with PLGA had been used:

- since the overall concentration of drug with respect to the polymer had decreased and
- the distance the drug had to cover to leave the matrix is increased,

the initial diffusion rate (first burst) would have been further reduced (with respect to the uncoated matrix), consequently leading to a much shorter release duration caused by an undesired much sooner destruction of the polymer both of the matrix and the coating.
In view of the fact that this eventuality is definitely not desirable as far as a long term release implants are expected, the skilled person would have once again considered absolutely unsuitable the PLGA, as polymer for long term release implants.

In view of this clear teaching away, it has been **absolutely unexpected** that implants having a core comprising at least one active principle dispersed in a polymeric matrix essentially consisting of **PLGA**, wherein said active principle is at most 55% mass/mass of the total weight of the core, **and** a coating comprising as the main component PLGA, wherein said core is wholly coated by said coating, show a very good linear release profile over a pretty prolonged period. This has been already made evident by all the given Examples, for instance, by Example 3 and related Figure 3B, where the **release profile** is advantageously **linear** and **do not show any burst** and the **entire release period** is observed to be about 350 days, i.e. **more than 11 months**!

I am, therefore, keenly convinced that the **implants** according to the current invention are **extremely inventive**, since the combination of claimed features of the currently pending **Claim 22** allows to achieve the **surprising and unexpected results** of a **very prolonged and linear drug release profile until the entire drug release**, with respect to all the prior art documents cited.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 19th March 2009

Patrice Mauriac